Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med 2017;377:1345-56. DOI: 10.1056/NEJMoa1709684

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Contents

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METHODS

Statistical analysis

Time-to-event distributions (survival rates) at fixed time points were estimated using Kaplan-Meier methods. Treatment differences for progression-free and overall survival were assessed using stratified log-rank test. Hazard ratios and corresponding 95% CIs were estimated with a stratified Cox proportional hazards model. All statistical testing and 95% CIs were two-sided. Overall survival analyses were also performed in prespecified subgroups of patients. Tumor PD-L1 expression was evaluated as a predictive biomarker for progression-free and overall survival using time-dependent receiver operating characteristic (ROC) curves for censored survival data in an attempt to evaluate the predictive accuracy of PD-L1 as a biomarker and to distinguish a discrimination threshold of PD-L1 expression for predicting OS.[1]

Figure S1. CONSORT flow diagram.

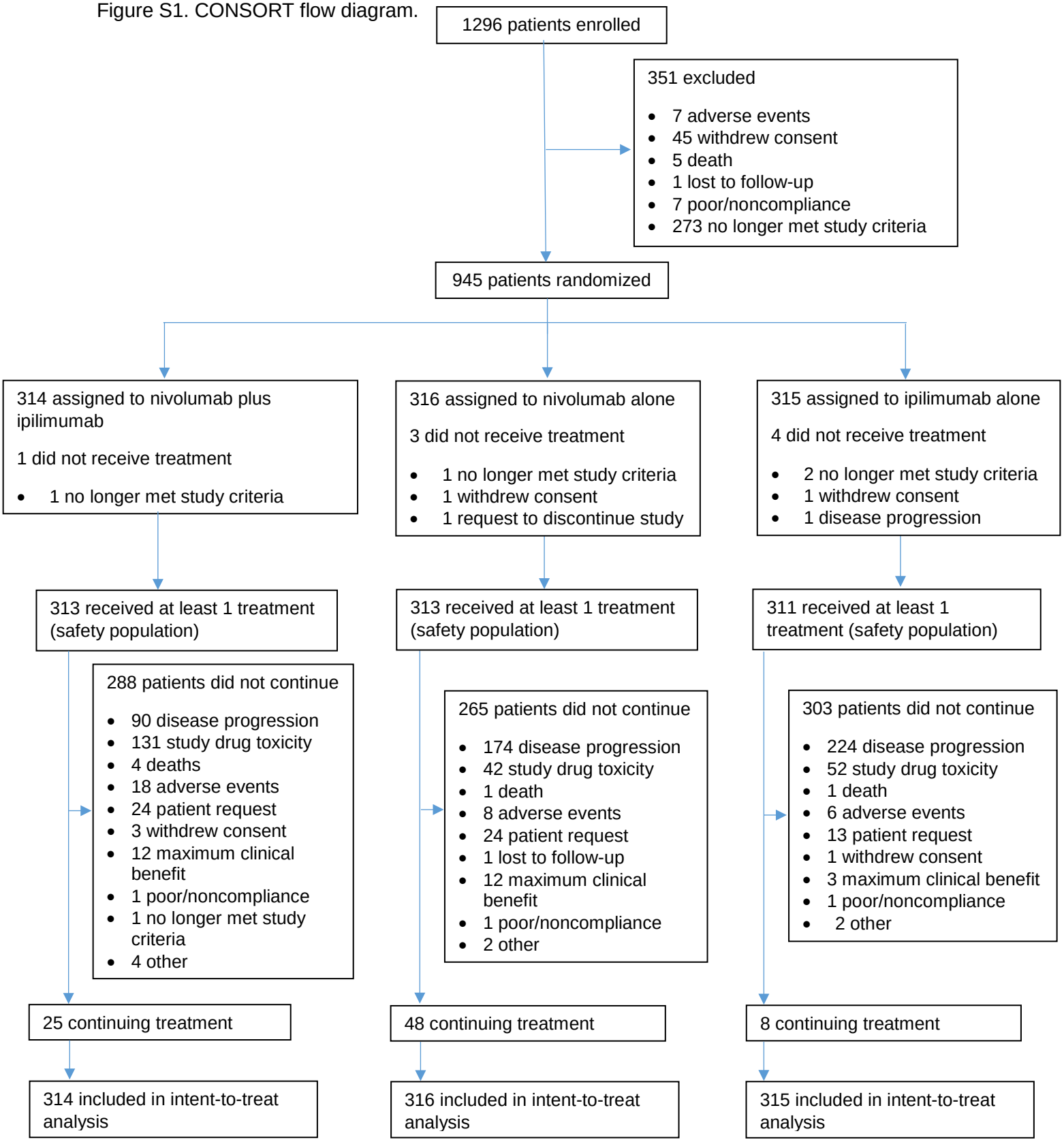
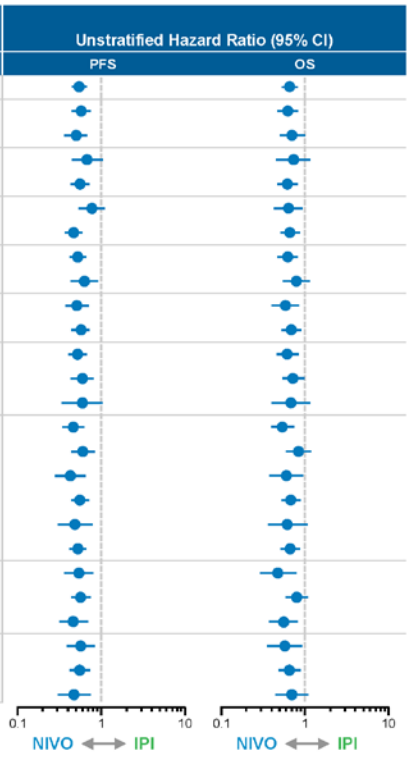


Figure S2. Forest plot of overall survival in prespecified subgroups of patients who received nivolumab versus ipilimumab (A) and combination versus ipilimumab (B). CI denotes confidence interval; ECOG PS Eastern Cooperative Oncology Group performance status; EU European Union; IPI ipilimumab; LDH lactate dehydrogenase; NIVO nivolumab; OS overall survival; PD-L1 programmed death ligand 1; PFS progression-free survival; ULN upper limit of normal; US United States.

(A)

Subgroup	Patients		3-Year Rate (PFS)		3-Year Rate (OS)		Unstratified Hazard Ratio	
	NIVO	IPI	NIVO	IPI	NIVO	IPI	PFS	OS
Overall	316	315	32	10	52	34	0.54	0.66
Age <65 years	198	182	31	9	51	33	0.58	0.62
Age ≥65 years	118	133	34	11	52	36	0.49	0.71
US	68	75	31	15	57	38	0.68	0.73
EU	170	170	28	10	49	29	0.56	0.62
BRAF Mutant	98	100	22	14	56	37	0.77	0.63
BRAF Wild-type	218	215	36	9	50	32	0.47	0.67
ECOG PS = 0	237	224	33	10	58	40	0.52	0.63
ECOG PS = 1	79	91	27	10	32	19	0.63	0.78
M0/M1a/M1b	132	127	39	10	64	44	0.51	0.58
M1c	184	188	27	10	42	27	0.57	0.69
LDH ≤ ULN	197	194	37	14	61	42	0.52	0.61
LDH > ULN	112	115	21	3	34	20	0.59	0.73
LDH > 2 x ULN	37	30	11	0	14	7	0.59	0.68
PD-L1 ≥1%	171	164	39	12	60	37	0.46	0.54
PD-L1 <1%	117	113	26	7	42	31	0.61	0.84
PD-L1 ≥5%	80	75	41	12	61	45	0.43	0.60
PD-L1 <5%	208	202	31	9	50	31	0.56	0.68
PD-L1 ≥10%	59	54	39	16	58	45	0.49	0.62
PD-L1 <10%	229	223	32	9	51	32	0.53	0.67
Tumor burden ≤Q1 (31 mm)	85	79	38	15	69	48	0.54	0.48
Tumor burden >Q1 and ≤Q3	150	167	30	9	48	36	0.57	0.79
Tumor burden >Q3 (97 mm)	80	69	29	5	39	13	0.47	0.55
Lesion sites: 1	80	84	37	12	65	48	0.57	0.58
Lesion sites: 2-3	176	170	28	9	48	29	0.55	0.66
Lesion sites: >3	59	61	36	11	44	28	0.47	0.70



(B)

Subgroup	Patients		3-Year Rate (PFS)		3-Year Rate (OS)		Unstratified Hazard Ratio		Unstratified Hazard Ratio (95% CI)	
	NIVO+IPI	IPI	NIVO+IPI	IPI	NIVO+IPI	IPI	PFS	OS	PFS	OS
Overall	314	315	39	10	58	34	0.43	0.56		
Age <65 years	185	182	39	9	61	33	0.42	0.48		
Age ≥65 years	129	133	37	11	54	36	0.45	0.69		
US	64	75	45	15	70	38	0.48	0.43		
EU	177	170	34	10	53	29	0.43	0.56		
BRAF Mutant	102	100	40	14	68	37	0.46	0.43		
BRAF Wild-type	212	215	38	9	53	32	0.42	0.62		
ECOG PS = 0	230	224	39	10	64	40	0.42	0.53		
ECOG PS = 1	83	91	37	10	43	19	0.47	0.64		
M0/M1a/M1b	129	127	50	10	72	44	0.34	0.46		
M1c	185	188	31	10	48	27	0.49	0.61		
LDH ≤ ULN	199	194	45	14	66	42	0.39	0.53		
LDH > ULN	114	115	28	3	44	20	0.47	0.61		
LDH > 2 x ULN	37	30	17	0	31	7	0.41	0.50		
PD-L1 ≥1%	155	164	43	12	62	37	0.42	0.55		
PD-L1 <1%	123	113	35	7	54	31	0.41	0.59		
PD-L1 ≥5%	68	75	49	12	65	45	0.36	0.59		
PD-L1 <5%	210	202	36	9	56	31	0.44	0.56		
PD-L1 ≥10%	46	54	58	16	67	45	0.30	0.51		
PD-L1 <10%	232	223	35	9	57	32	0.44	0.58		
Tumor burden ≤Q1 (31 mm)	78	79	45	15	72	48	0.39	0.46		
Tumor burden >Q1 and ≤Q3	154	167	38	9	59	36	0.44	0.59		
Tumor burden >Q3 (97 mm)	82	69	33	5	41	13	0.42	0.51		
Lesion sites: 1	89	84	47	12	70	48	0.37	0.51		
Lesion sites: 2-3	166	170	38	9	57	29	0.41	0.53		
Lesion sites: >3	59	61	27	11	42	28	0.59	0.74		

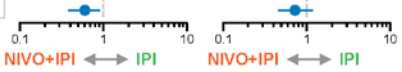
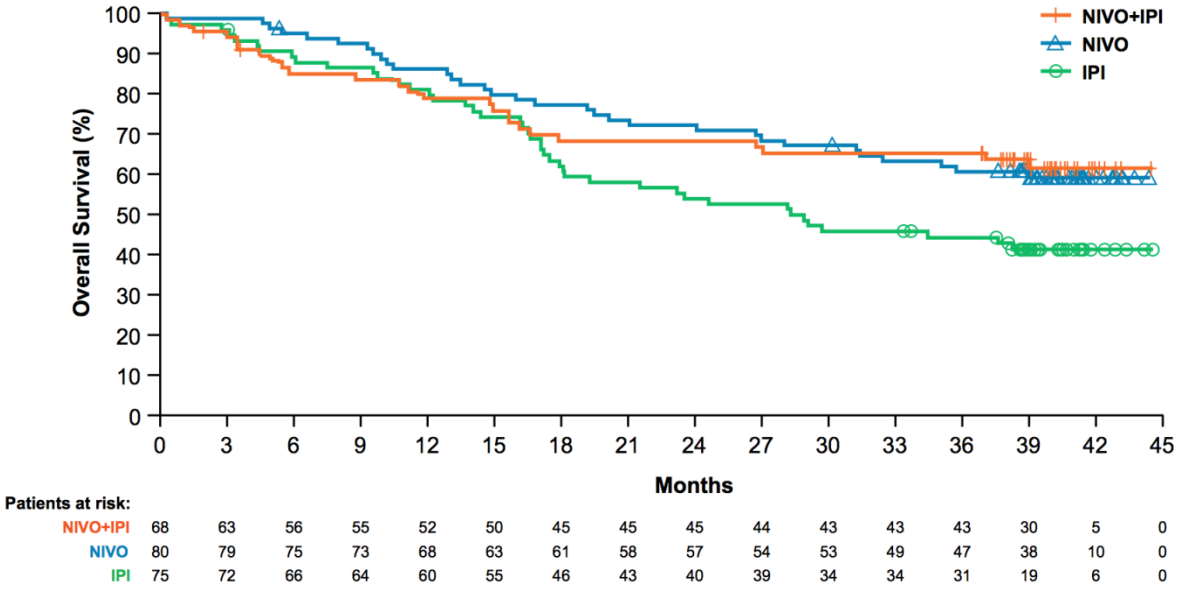


Figure S3. Overall survival by PD-L1 expression at 5% and 1% cutoffs. Panel A shows the Kaplan-Meier estimates of overall survival in patients with PD-L1 expression level ≥5%. Median overall survival was not reached (95% CI, 39.1 to not reached) in the combination group, not reached (95% CI, 35.8 to not reached) in the nivolumab group, and 28.9 months (95% CI, 18.1 to not reached) in the ipilimumab group. Panel B shows the Kaplan-Meier estimates of overall survival in patients with PD-L1 expression <5%. Median overall survival was not reached (95% CI, 32.7 to not reached) in the combination group, 35.9 months (95% CI, 23.1 to not reached) in the nivolumab group, and 18.4 months (95% CI, 13.7 to 22.5) in the ipilimumab group. Panel C shows the Kaplan-Meier estimates of overall survival in patients with PD-L1 expression level ≥1%. Median overall survival was not reached (95% CI, 39.1 to not reached) in the combination group, not reached (95% CI, 40.2 to not reached) in the nivolumab group, and 21.5 months (95% CI, 16.9 to 29.1) in the ipilimumab group. Panel D shows the Kaplan-Meier estimates of overall survival in patients with PD-L1 expression <1%. Median overall survival was not reached (95% CI, 26.5 to not reached) in the combination group, 23.5 months (95% CI, 13.0 to 36.5) in the nivolumab group, and 18.6 months (95% CI, 13.7 to 23.2) in the ipilimumab group. CI denotes confidence interval; IPI ipilimumab; NIVO nivolumab; PD-L1 programmed death ligand 1.

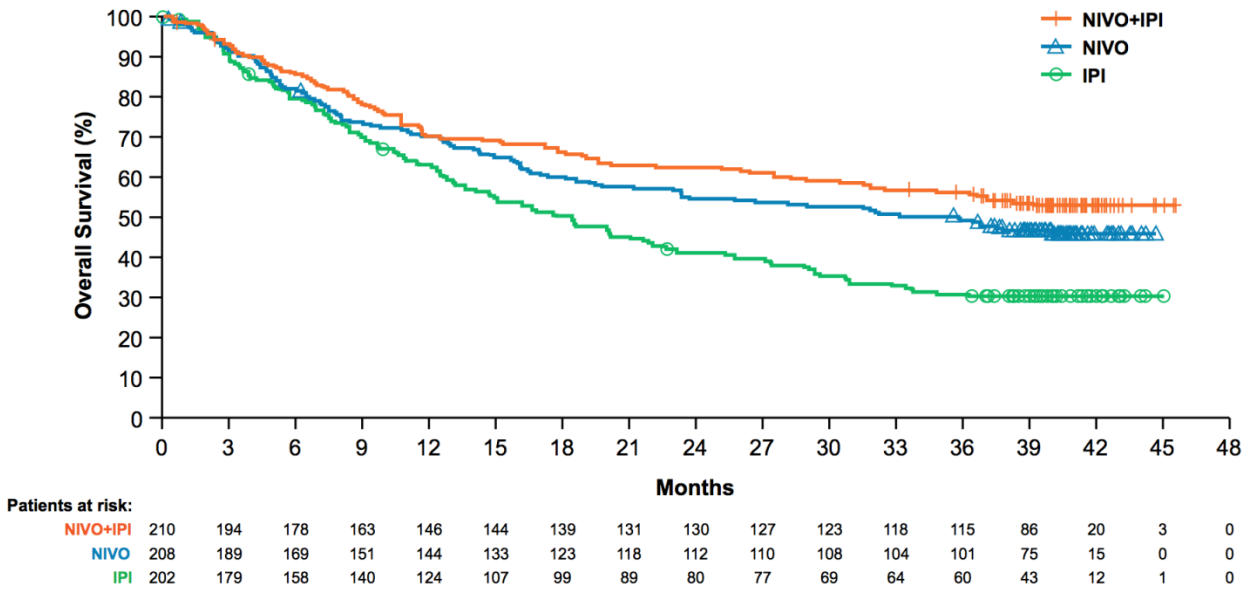
(A) PD-L1 expression level ≥5%



Patients at risk:

NIVO+IPI	68	63	56	55	52	50	45	45	45	44	43	43	43	30	5	0
NIVO	80	79	75	73	68	63	61	58	57	54	53	49	47	38	10	0
IPI	75	72	66	64	60	55	46	43	40	39	34	34	31	19	6	0

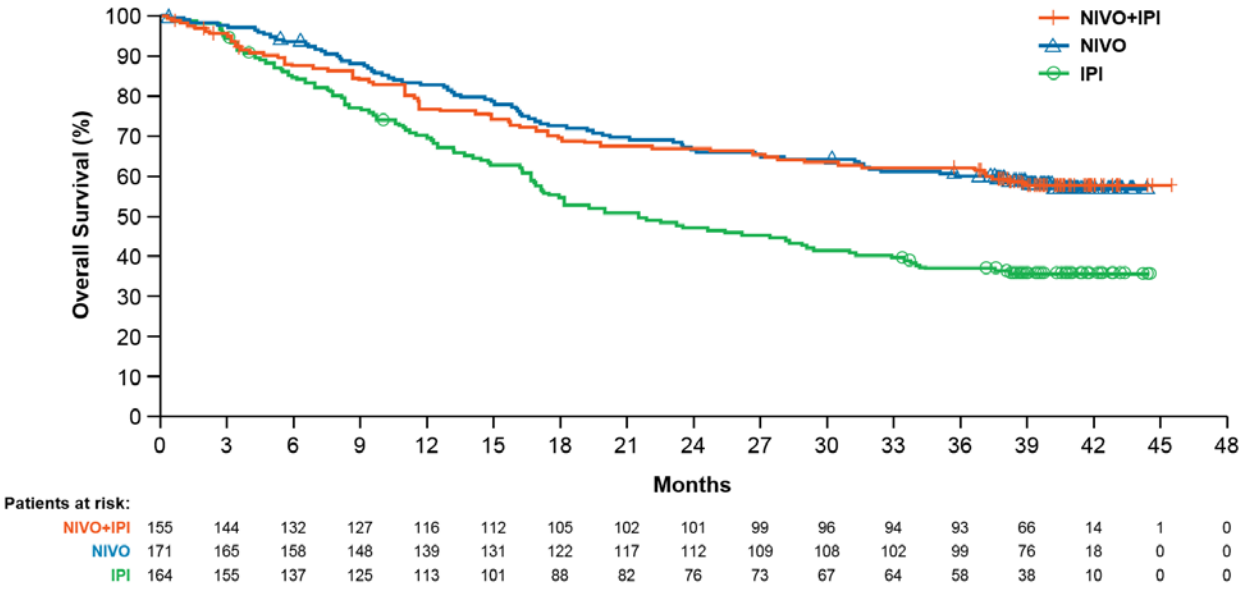
(B) PD-L1 expression level <5%



Patients at risk:

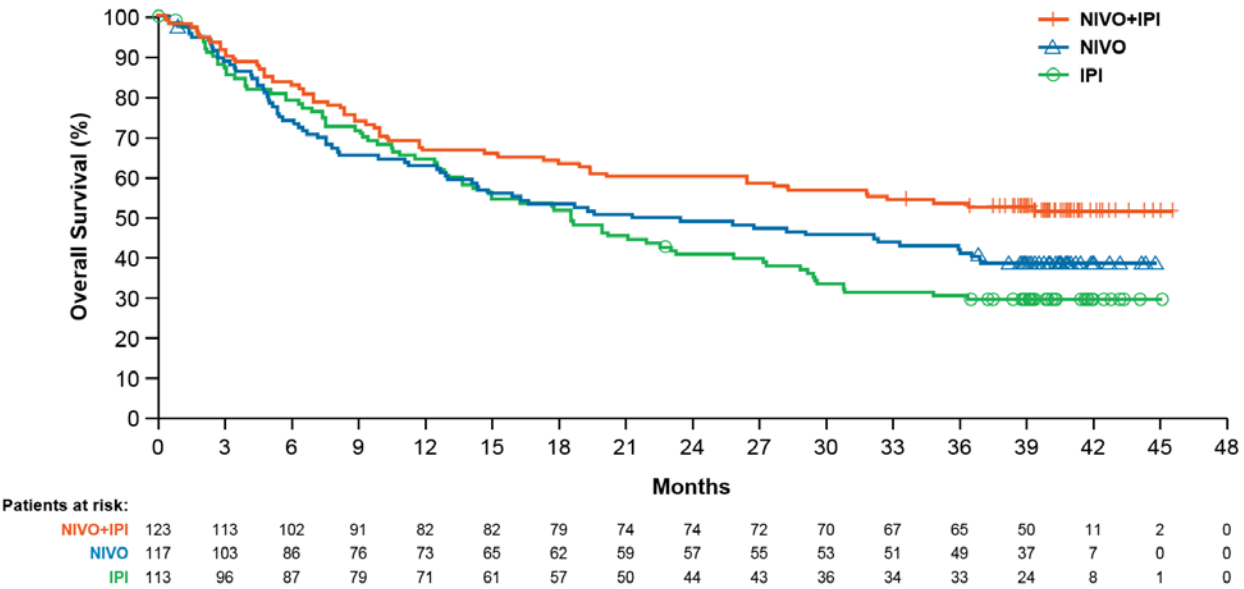
NIVO+IPI	210	194	178	163	146	144	139	131	130	127	123	118	115	86	20	3	0
NIVO	208	189	169	151	144	133	123	118	112	110	108	104	101	75	15	0	0
IPI	202	179	158	140	124	107	99	89	80	77	69	64	60	43	12	1	0

(C) PD-L1 expression level ≥1%



Patients at risk:																
NIVO+IPI	155	144	132	127	116	112	105	102	101	99	96	94	93	66	14	1	0
NIVO	171	165	158	148	139	131	122	117	112	109	108	102	99	76	18	0	0
IPI	164	155	137	125	113	101	88	82	76	73	67	64	58	38	10	0	0

(D) PD-L1 expression level <1%



Patients at risk:																
NIVO+IPI	123	113	102	91	82	82	79	74	74	72	70	67	65	50	11	2	0
NIVO	117	103	86	76	73	65	62	59	57	55	53	51	49	37	7	0	0
IPI	113	96	87	79	71	61	57	50	44	43	36	34	33	24	8	1	0

Figure S4. Three-year overall survival data based on PD-L1 expression using time-dependent ROC for censored survival data. Post hoc analyses were performed on all randomized patients with quantifiable PD-L1 expression (N=278 for nivolumab plus ipilimumab; N=288 for nivolumab alone). AUC values were 0.56 (95% CI, 0.49 to 0.63) and 0.57 (95% CI, 0.50 to 0.63) for the combination and nivolumab groups, respectively. In an ROC analysis, an AUC=1 is an idealized result showing complete discrimination of the ability of a test to predict an outcome; AUC ≥0.8 is considered a test with good discriminatory ability; and a line representing no discrimination at all would be at AUC = 0.5.[1,2] AUC denotes area under the curve; CI confidence interval; PD-L1 programmed death 1; ROC receiver operating characteristic.

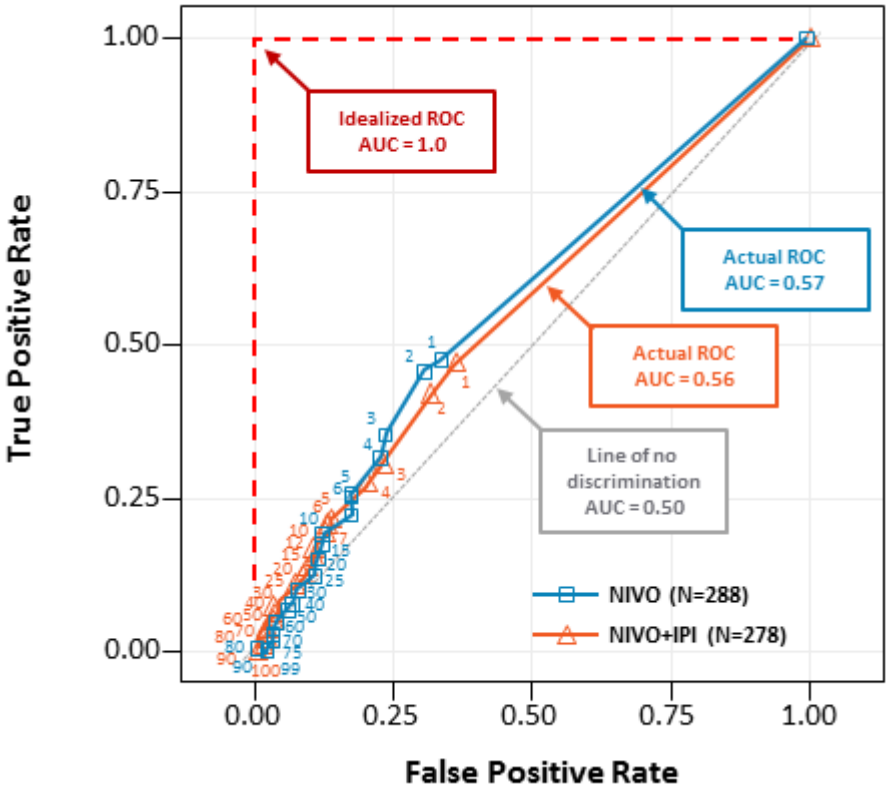


Table S1. Baseline Characteristics of the Randomized Patients.

Characteristic	Nivolumab Plus Ipilimumab (N=314)	Nivolumab Alone (N=316)	Ipilimumab Alone (N=315)
Median age, year (range)	61 (18–88)	60 (25–90)	62 (18–89)
Sex, n (%)			
Male	206 (66)	202 (64)	202 (64)
Female	108 (34)	114 (36)	113 (36)
ECOG performance status, n (%)			
0	230 (73)	238 (75)	224 (71)
1	83 (26)	77 (24)	91 (29)
2	0	1 (<1)	0
Not reported	1 (<1)	0	0
M stage, n (%)			
M1c	181 (58)	184 (58)	183 (58)
M0, M1a, or M1b	133 (42)	132 (42)	132 (42)
Lactate dehydrogenase, n (%)			
≤ULN	199 (63)	196 (62)	194 (62)
>ULN	114 (36)	112 (35)	115 (37)
≤2× ULN	276 (88)	271 (86)	279 (89)
>2× ULN	37 (12)	37 (12)	30 (10)
Unknown	1 (<1)	8 (3)	6 (2)
Brain metastases at baseline, n (%)			
Yes	11 (4)	8 (3)	15 (5)
No	303 (97)	308 (98)	300 (95)
PD-L1 status, n (%)			
Positive	68 (22)	80 (25)	75 (24)
Negative	210 (67)	208 (66)	202 (64)
Indeterminate or not evaluable	36 (11)	28 (9)	38 (12)
BRAF status, n (%)			
Mutation	101 (32)	100 (32)	97 (31)
No mutation	213 (68)	216 (68)	218 (69)
Sum of reference diameters of target lesions (mm), median (range)	54.5 (10–372)	54.0 (10–384)	55.0 (10–283)
Number of lesion sites, n (%)			
1	89 (28)	80 (25)	84 (27)
2-3	166 (53)	176 (56)	170 (54)
>3	59 (19)	59 (19)	61 (19)

ECOG denotes Eastern Cooperative Oncology Group; PD-L1 programmed death ligand 1; ULN upper limit of normal.

Table S2. Subsequent Therapy.

	Nivolumab Plus Ipilimumab (N=314)	Nivolumab (N=316)	Ipilimumab (N=315)
Any subsequent therapy, n (%)	132 (42)	176 (56)	229 (73)
Subsequent systemic therapy	101 (32)	145 (46)	199 (63)
Subsequent immunotherapy	48 (15)	99 (31)	140 (44)
Anti-PD-1 agents	32 (10)	44 (14)	134 (43)
Anti-PD-L1 agents	0	0	2 (1)
Anti-CTLA-4 agents	19 (6)	88 (28)	14 (4)
Other immunotherapy	5 (2)	11 (4)	10 (3)
BRAF inhibitor	41 (13)	59 (19)	71 (23)
MEK/NRAS inhibitor	31 (10)	40 (13)	40 (13)
Other approved agents	44 (14)	59 (19)	69 (22)
Other investigational agent	8 (3)	8 (3)	15 (5)
Subsequent radiotherapy, n (%)	58 (19)	88 (28)	121 (38)
Subsequent surgery, n (%)	58 (19)	61 (19)	87 (28)
Median time to subsequent systemic therapy, months (95% CI)	NR	25.5 (16.3–NR)	8.1 (6.5–8.8)
Patients free of subsequent therapy at 3 years, % (95% CI)*	59% (53%–65%)	45% (39%–51%)	20% (15%–26%)

*Excluding patients who died and never received subsequent therapy; based on Kaplan-Meier estimates.

CI denotes confidence interval; CTLA-4 cytotoxic T-lymphocyte antigen 4; NR not reached; PD-1 programmed death 1; PD-L1 programmed death ligand 1.

Table S3. Post-treatment Tumor Assessments in All Randomized Patients With Progressive Disease.

	Nivolumab Plus Ipilimumab (N=74)	**Nivolumab (N=121)**	**Ipilimumab (N=159)**
Patients with at least one existing lesion, n (%)	18 (24)	31 (26)	39 (25)
Patients with at least one new lesion, n (%)	56 (76)	90 (74)	120 (75)
Site of new lesion, n (%)			
Bone	12 (16)	11 (9)	12 (8)
Central nervous system	8 (11)	21 (17)	23 (14)
Intestine	4 (5)	5 (4)	5 (3)
Liver	10 (14)	25 (21)	38 (24)
Lung	17 (23)	29 (24)	46 (29)
Lymph node	8 (11)	15 (12)	27 (17)
Other	5 (7)	4 (3)	9 (6)
Skin	3 (4)	10 (8)	8 (5)
Soft tissue	8 (11)	15 (12)	21 (13)
Visceral, other	7 (9)	18 (15)	30 (19)
No. of sites with at least one new lesion, n (%)			
1	35 (47)	53 (44)	57 (36)
2	16 (22)	18 (15)	36 (23)
3	5 (7)	13 (11)	19 (12)
4	0	5 (4)	7 (4)
≥5	0	1 (1)	1 (1)

Table S4. Response to Treatment by PD-L1 Expression.

	Nivolumab Plus Ipilimumab	**Nivolumab**	**Ipilimumab**
≥1% PD-L1, n	155	171	164
CR, n (%)	32 (21)	36 (21)	8 (5)
PR, n (%)	68 (44)	57 (33)	23 (14)
ORR, % (95% CI)	65 (56.4–72.0)	54 (46.6–62.0)	19 (13.2–25.7)
<1% PD-L1, n	123	117	113
CR, n (%)	24 (20)	16 (14)	7 (6)
PR, n (%)	42 (34)	25 (21)	13 (12)
ORR, % (95% CI)	54 (44.4–62.7)	35 (26.5–44.4)	18 (11.2–26.0)
≥5% PD-L1, n	68	80	75
CR, n (%)	15 (22)	18 (23)	5 (7)
PR, n (%)	34 (50)	28 (35)	11 (15)
ORR, % (95% CI)	72 (59.9–82.3)	58 (45.9–68.5)	21 (12.7–32.3)
<5% PD-L1, n	210	208	202
CR, n (%)	41 (20)	34 (16)	10 (5)
PR, n (%)	76 (36)	54 (26)	25 (12)
ORR, % (95% CI)	56 (48.7–62.5)	42 (35.5–49.3)	17 (12.4–23.3)
≥10% PD-L1, n	46	59	54
CR, n (%)	13 (28)	11 (19)	3 (6)
PR, n (%)	26 (57)	23 (39)	8 (15)
ORR, % (95% CI)	85 (71.1–93.7)	58 (44.1–70.4)	20 (10.6–33.5)
<10% PD-L1	232	229	223
CR, n (%)	43 (19)	41 (18)	12 (5)
PR, n (%)	84 (36)	59 (26)	28 (13)
ORR, % (95% CI)	55 (48.1–61.3)	44 (37.1–50.4)	18 (13.1–23.6)

CI denotes confidence interval; CR complete response; ORR objective response rate; PD-L1 programmed death ligand 1; PR partial response.

Table S5. Treatment-related AEs of Any Grade in ≥5% of Patients in any Treatment Group.*

	Nivolumab Plus Ipilimumab (N=313)		**Nivolumab (N=313)**		**Ipilimumab† (N=311)**	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Any treatment-related AE	300 (96)	184 (59)	270 (86)	67 (21)	268 (86)	86 (28)
Rash	93 (30)	10 (3)	72 (23)	1 (<1)	68 (22)	5 (2)
Pruritus	112 (36)	6 (2)	67 (21)	1 (<1)	113 (36)	1 (<1)
Vitiligo	28 (9)	0	29 (9)	1 (<1)	16 (5)	0
Dry skin	15 (5)	0	17 (5)	0	11 (4)	0
Maculopapular rash	38 (12)	6 (2)	15 (5)	2 (1)	38 (12)	1 (<1)
Fatigue	119 (38)	13 (4)	114 (36)	3 (1)	89 (29)	3 (1)
Asthenia	30 (10)	1 (<1)	25 (8)	1 (<1)	17 (5)	2 (1)
Pyrexia	60 (19)	2 (1)	21 (7)	0	21 (7)	1 (<1)
Chills	22 (7)	0	12 (4)	0	10 (3)	0
Diarrhea	142 (45)	29 (9)	67 (21)	9 (3)	105 (34)	18 (6)
Nausea	88 (28)	7 (2)	41 (13)	0	51 (16)	2 (1)
Vomiting	48 (15)	7 (2)	22 (7)	1 (<1)	24 (8)	1 (<1)
Constipation	12 (4)	0	20 (6)	0	16 (5)	0
Abdominal pain	26 (8)	1 (<1)	18 (6)	0	28 (9)	2 (1)
Dry mouth	19 (6)	0	13 (4)	0	7 (2)	0
Colitis	40 (13)	26 (8)	7 (2)	3 (1)	35 (11)	24 (8)
Headache	35 (11)	2 (1)	24 (8)	0	25 (8)	1 (<1)
Dysgeusia	14 (4)	0	18 (6)	0	9 (3)	0
Dizziness	18 (6)	0	15 (5)	0	12 (4)	0
Arthralgia	43 (14)	2 (1)	31 (10)	1 (<1)	22 (7)	0
Myalgia	17 (5)	1 (<1)	16 (5)	1 (<1)	9 (3)	0
Increased lipase	44 (14)	34 (11)	27 (9)	14 (4)	18 (6)	12 (4)
Increased amylase	26 (8)	9 (3)	20 (6)	6 (2)	15 (5)	4 (1)
Increased aspartate aminotransferase	51 (16)	19 (6)	14 (4)	3 (1)	12 (4)	2 (1)
Increased alanine aminotransferase	60 (19)	27 (9)	13 (4)	4 (1)	12 (4)	5 (2)
Decreased weight	19 (6)	0	10 (3)	0	4 (1)	1 (<1)
Hypothyroidism	53 (17)	1 (<1)	33 (11)	0	14 (5)	0
Hyperthyroidism	35 (11)	3 (1)	14 (4)	0	3 (1)	0
Hypophysitis	23 (7)	5 (2)	2 (1)	1 (<1)	12 (4)	5 (2)
Decreased appetite	60 (19)	4 (1)	36 (12)	0	41 (13)	1 (<1)
Cough	25 (8)	0	19 (6)	2 (1)	15 (5)	0
Dyspnea	36 (12)	3 (1)	19 (6)	1 (<1)	12 (4)	0
Pneumonitis	22 (7)	3 (1)	5 (2)	1 (<1)	5 (2)	1 (<1)
Treatment-related AE leading to discontinuation	123 (39)	95 (30)	37 (12)	24 (8)	49 (16)	43 (14)

*Data are n (%). The severity of AEs was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. AE denotes adverse event.

†One patient in the ipilimumab group died due to cardiac arrest.

Table S6. Treatment-related Adverse Events of Potential Immunologic Etiology (Select Adverse Events) in ≥2% of Patients.

Patients Reporting Event	Nivolumab Plus Ipilimumab (N=313)		Nivolumab (N=313)		Ipilimumab (N=311)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Skin and subcutaneous	193 (62)	20 (6)	144 (46)	7 (2)	173 (56)	9 (3)
Rash	93 (30)	10 (3)	72 (23)	1 (<1)	68 (22)	5 (2)
Pruritus	112 (36)	6 (2)	67 (21)	1 (<1)	113 (36)	1 (<1)
Vitiligo	28 (9)	0	29 (9)	1 (<1)	16 (5)	0
Maculopapular rash	38 (12)	6 (2)	15 (5)	2 (1)	38 (12)	1 (<1)
Erythema	6 (2)	1 (<1)	9 (3)	0	5 (2)	1 (<1)
Dermatitis	5 (2)	0	8 (3)	0	2 (1)	0
Skin hypopigmentation	6 (2)	0	7 (2)	0	2 (1)	0
Eczema	9 (3)	0	6 (2)	0	2 (1)	0
Papular rash	7 (2)	0	4 (1)	1 (<1)	4 (1)	0
Generalized rash	8 (3)	1 (<1)	2 (1)	0	2 (1)	1 (<1)
Macular rash	7 (2)	0	2 (1)	0	1 (<1)	1 (<1)
Pruritic rash	5 (2)	0	1 (<1)	0	7 (2)	0
Gastrointestinal	150 (48)	47 (15)	70 (22)	11 (4)	117 (38)	36 (12)
Diarrhea	142 (45)	29 (9)	67 (21)	9 (3)	105 (34)	18 (6)
Colitis	40 (13)	26 (8)	7 (2)	3 (1)	35 (11)	24 (8)
Endocrine	106 (34)	20 (6)	54 (17)	5 (2)	36 (12)	8 (3)
Hypothyroidism	53 (17)	1 (<1)	33 (11)	0	14 (5)	0
Hyperthyroidism	35 (11)	3 (1)	14 (4)	0	3 (1)	0
Adrenal insufficiency	11 (4)	6 (2)	4 (1)	2 (1)	4 (1)	1 (<1)
Thyroiditis	13 (4)	1 (<1)	3 (1)	0	1 (<1)	0
Hypophysitis	23 (7)	5 (2)	2 (1)	1 (<1)	12 (4)	5 (2)
Hepatic	102 (33)	62 (20)	25 (8)	9 (3)	23 (7)	5 (2)
Increased aspartate aminotransferase	51 (16)	19 (6)	14 (4)	3 (1)	12 (4)	2 (1)
Increased alanine aminotransferase	60 (19)	27 (9)	13 (4)	4 (1)	12 (4)	5 (2)
Increased blood alkaline phosphatase	12 (4)	2 (1)	4 (1)	0	2 (1)	1 (<1)
Increased transaminases	12 (4)	10 (3)	2 (1)	1 (<1)	3 (1)	0
Increased gamma-glutamyltransferase	10 (3)	4 (1)	1 (<1)	0	6 (2)	1 (<1)

Hepatotoxicity	10 (3)	8 (3)	1 (<1)	1 (<1)	1 (<1)	0
Hyperbilirubinemia	7 (2)	0	1 (<1)	0	3 (1)	0
Hepatitis	7 (2)	5 (2)	0	0	0	0
Hypersensitivity/ infusion reactions	13 (4)	0	14 (4)	1 (<1)	8 (3)	1 (<1)
Infusion-related reaction	9 (3)	0	8 (3)	1 (<1)	8 (3)	1 (<1)
Hypersensitivity	9 (3)	0	6 (2)	0	8 (3)	1 (<1)
Pulmonary	24 (8)	3 (1)	6 (2)	1 (<1)	6 (2)	1 (<1)
Pneumonitis	22 (7)	3 (1)	5 (2)	1 (<1)	5 (2)	1 (<1)
Renal	22 (7)	6 (2)	4 (1)	1 (<1)	8 (3)	1 (<1)
Increased blood creatinine	14 (4)	1 (<1)	2 (1)	1 (<1)	5 (2)	0

Table S7. Time to Resolution of Treatment-related Select AEs in Patients Who Received Immune-modulating Medication.[a]

	Nivolumab Plus Ipilimumab (N=313)			**Nivolumab (N=313)**			**Ipilimumab (N=311)**		
	No. (%) Patients With Select AE	No. (%) of Patients With Resolution of AE[b]	Median Time to Resolution, Weeks (range)	No. (%) Patients With Select AE	No. (%) of Patients With Resolution of AE[b]	Median Time to Resolution, Weeks (range)	No. (%) Patients With Select AE	No. (%) of Patients With Resolution of AE[b]	Median Time to Resolution, Weeks (range)
Skin	70/193 (36)	54/70 (77)	8.9 (0.7–184.7+)	44/144 (31)	26/44 (59)	39.6 (1.1–186.1+)	58/173 (34)	49/58 (84)	12.4 (0.9–179.6+)
Grade 3-5	15/20 (75)	15/15 (100)	3.1 (0.6–54.6)	5/7 (71)	4/5 (80)	3.0 (0.9–111.0+)	6/9 (67)	6/6 (100)	6.1 (4.4–27.3)
Gastrointestinal	68/150 (45)	65/68 (96)	4.2 (0.3–197.1+)	10/70 (14)	7/10 (70)	7.2 (0.9–128.4+)	51/117 (44)	47/51 (92)	4.9 (1.1–107.7)
Grade 3-5	44/47 (94)	43/44 (98)	3.0 (0.3–33.1+)	8/11 (73)	5/8 (63)	12.4 (0.9–128.4+)	35/36 (97)	33/35 (94)	3.9 (0.4–107.7)
Endocrine	40/106 (38)	17/40 (43)	NA (0.4–190.7+)	7/54 (13)	2/7 (29)	NA (8.3–154.0+)	16/36 (44)	5/16 (31)	NA (0.6–176.1+)
Grade 3-5	14/20 (70)	7/14 (50)	18.6 (1.6–161.4+)	3/5 (60)	0/3 (0)	NA (125.7+–154.0+)	8/8 (100)	4/8 (50)	NA (0.7–160.7+)
Hepatic	46/102 (45)	45/46 (98)	5.9 (0.3–106.9)	6/25 (24)	6/6 (100)	7.0 (2.0–27.1)	3/23 (13)	3/3 (100)	4.1 (4.0–7.7)
Grade 3-5	38/62 (61)	38/38 (100)	4.1 (0.3–26.0)	6/9 (67)	6/6 (100)	7.0 (2.0–27.1)	2/5 (40)	2/2 (100)	5.9 (4.0–7.7)
Hypersensitivity/ infusion reactions	1/13 (8)	1/1 (100)	0.14 (0.1–0.1)	3/14 (21)	3/3 (100)	0.14 (0.1–0.7)	1/8 (13)	1/1 (100)	0.3 (0.3–0.3)
Grade 3-5	0	0	--	0/1	0	--	1/1 (100)	1/1(100)	0.3 (0.3–0.3)
Pulmonary	18/24 (75)	18/18 (100)	6.1 (0.9–35.1)	5/6 (83)	4/5 (80)	2.4 (0.6–70.0+)	3/6 (50)	2/3 (67)	6.1 (4.3+–6.3)
Grade 3-5	2/3 (67)	2/2 (100)	4.2 (1.1–7.3)	1/1 (100)	1/1 (100)	2.3 (2.3–2.3)	1/1 (100)	1/1 (100)	4.7 (4.7–4.7)
Renal	4/22 (18)	4/4 (100)	2.7 (0.4–13.7)	2/4 (50)	1/2 (50)	NA (0.3–118.1+)	3/8 (38)	3/3 (100.0)	4.6 (0.6–16.1)
Grade 3-5	3/6 (50)	3/3 (100)	1.7 (0.4–3.6)	0/1	0	NA	1/1 (100)	1/1 (100)	4.6 (4.6–4.6)

[a]Restricted to patients who received immune-modulating medication during their select AE of longest duration. Includes events reported between the first dose and 30 days after the last dose of study therapy. AE denotes adverse event; NA not available.

[b]The total number of patients with resolution of event was the number of treated patients experiencing resolution or improvement to the baseline grade for the longest AE belonging to the select AE category.

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